PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number:	WO 90/01933
A61K 31/56	A1	(43) International Publication Date:	8 March 1990 (08.03.90)

(21) International Application Number: PCT/US89/03648

(22) International Filing Date: 24 August 1989 (24.08.89)

(30) Priority data:
236,828 26 August 1988 (26.08.88) US

(71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(72) Inventor: CAGLE, Gerald, D. ; 4224 Buttonwood Road, Fort Worth, TX 76133 (US).

(74) Agent: PRICE, Robert, L.; Lowe, Price, LeBlanc, Becker & Shur, Suite 300, 99 Canal Center Plaza, Alexandria, VA 22314 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMBINATION OF QUINOLONE ANTIBIOTICS AND STEROIDS FOR TOPICAL OPHTHALMIC USE

(57) Abstract

Disclosed are pharmaceutical compositions containing a quinolone antibiotic, such as ciprofloxacin, and a steroid, such as rimexolone, dexamethasone, fluorometholone or fluorometholone acetate, and the like for topical ophthalmic delivery, and a method of treatment comprising administering said compositions topically to the affected ocular tissue when indicated for control of infection and associated inflammation.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number: WO 90/01933
A61K 31/56	A1	(43) International Publication Date: 8 March 1990 (08.03.90)

(21) International Application Number: PCT/US89/03648

(22) International Filing Date: 24 August 1989 (24.08.89)

(30) Priority data:
236,828 26 August 1988 (26.08.88) US

(71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(72) Inventor: CAGLE, Gerald, D. ; 4224 Buttonwood Road, Fort Worth, TX 76133 (US).

(74) Agent: PRICE, Robert, L.; Lowe, Price, LeBlanc, Becker & Shur, Suite 300, 99 Canal Center Plaza, Alexandria, VA 22314 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMBINATION OF QUINOLONE ANTIBIOTICS AND STEROIDS FOR TOPICAL OPHTHALMIC USE

(57) Abstract

Disclosed are pharmaceutical compositions containing a quinolone antibiotic, such as ciprofloxacin, and a steroid, such as rimexolone, dexamethasone, fluorometholone or fluorometholone acetate, and the like for topical ophthalmic delivery, and a method of treatment comprising administering said compositions topically to the affected ocular tissue when indicated for control of infection and associated inflammation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Fasso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	HU	Hungary	NO	Norway
BJ	Benin	IT	Italy	RO	Romania
BR	Brazil	JP	Japan	SD	Sudan
CA	Canada	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic			SN	Senegal
CG	Congo	KR	Republic of Korea	SU	Soviet Union
CH	Switzerland	LI	Liechtenstein	TD	Chad
CM	Cameroon	LK	Sri Lanka	TG	Togo
DE	Germany, Federal Republic of	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

COMBINATION OF QUINOLONE ANTIBIOTICS AND STEROIDS FOR TOPICAL OPHTHALMIC USE

BACKGROUND OF THE INVENTION

The present invention relates to the topical ophthalmic use of antibiotics in combination with anti-inflammatory steroids to treat ophthalmic infections and attendant inflammation of ocular tissue. Such combinations are generally known and commercially available in the ophthalmic pharmaceutical art. However, there are concerns and expressed reservations in the ophthalmic community about the safety and efficacy of such prior art combinations. There is, moreover, a long felt need for effective and safe topical ophthalmic pharmaceutical compositions containing a potent steroid and a broad spectrum antibiotic which, when administrated to the eye when indicated for bacterial infection or as a prophylactic after ophthalmic trauma and injury, will not, as a possible expression of the steroid component, inhibit the activity of the antibiotic or interfere with normal wound healing, but at the same time will control inflammation. Unexpectedly it has been discovered that combinations of broad spectrum quinolone antibiotics such as ciprofloxacin, norfloxacin, oflaxacin, difloxacin, pefloxacin or the like and potent steroids such as dexamethasone, fluorometholone, fluorometholone acetate, prednisolone, prednisolone acetate, medrysone, betamethasone and rimexolone or the like, including pharmaceutically acceptable salts thereof, meet these

criteria. The foregoing antibiotics and steroids are known. A preferred antibiotic is ciprofloxacin. Preferred steroids include dexamethasone and rimexolone; the latter compound is described in U. S. Patent No. 3,947,478, the entire contents of which are hereby incorporated in the present specification by reference.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention are administered topically. The dosage range is 0.001 to 5.0 mg/per eye; wherein the cited mass figures present the sum of the two components, e.g. the steroid and the quinolone antibiotic. The compositions of the present invention can be administered as ointments, solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the mixtures are preferably formulated as 0.01 to 2.0 percent by weight (figures relate to combined presence of the steroid and quinolone antibiotic) solutions in water at a pH of 4.5 to 8.0., While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to

prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

Co-Solvents:

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80. Pluronic F-68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents:

Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compounds, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The following examples are presented to further illustrate representative topical ophthalmic pharmaceutical compositions of the present invention.

Example I

Ingredient	Amount	Wt. %
Dexamethasone, Micronized USP	1.0 mg + 5% excess	0.10% + 5% excess
Ciprofloxacin, USP	3.0 mg + 5% excess	0.30% + 5% excess
Benzalkonium Chloride Solution (10%), NF	0.001 ml+10% excess	0.10% + 10% excess[1]
Edetate Disodium, USP	0.1 mg	0.01%
Sodium Chloride, USP	3.0 mg	0.3%
Sodium Sulfate, USP	12.0 mg	1.2%
Tyloxapol, USP	0.5 mg	0.05%
Hydroxyethylcellulose	2.5 mg	0.25%
Sulfuric Acid and/or Sodium Hydroxide, NF	QS for pH adjustment	to 5.5 ± 0.5
Purified Water, USP	QS to 1 ml	QS to 100%

[1] The benzalkonium chloride, NF concentration is equivalent to 0.01% (+ 10% excess).

Example II

Ingredient	Amount	Wt. %
Fluorometholone Acetate, USP	1 mg + 2% excess	0.1% + 2% excess
Ciprofloxacin, USP	3 mg + 7% excess	0.3% + 7% excess
Chlorobutanol, Anhydrous, NF	5 mg + 15% excess	0.5 % + 25% excess
Mineral Oil, USP	50 mg	5%
White Petrolatum, USP	QS 1 g	QS 100%

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

Claims

1. An antibiotic/antiinflammatory ophthalmic pharmaceutical composition for topical delivery to the eye, comprising a therapeutically effective amount of an antibiotic selected from ciprofloxacin, norfloxacin, ofloxacin, difloxacin and pefloxacin; a therapeutically effective amount of an antiinflammatory steroid selected from dexamethasone, prednisolone, prednisolone acetate, medysone, fluormetholone, fluorometholone acetate, rimexolone, and betamethasone; and a pharmaceutically acceptable vehicle therefor.

2. An antibiotic/antiinflammatory ophthalmic pharmaceutical composition according to Claim 1, wherein the ratio of the antibiotic to the steroid is in the range of from 0.1:1.0 to 10.0:1.0.

3. A composition according to Claim 1 wherein the antibiotic comprises ciprofloxacin.

4. A composition according to Claim 1 wherein the steroid is selected from dexamethasone, fluorometholone and rimexolone.

5. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid is selected from dexamethasone, fluorometholone and rimexolone.

6. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises rimexolone.

7. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises dexamethasone.

8. A composition according to Claim 1, wherein the antibiotic comprises ciprofloxacin and the steroid comprises fluorometholone.

9. A method of treating infection and inflammation of ocular tissue which comprises applying an effective amount of a composition according to Claim 1 topically to the affected ocular tissue.

10. A method according to Claim 9, wherein the composition comprises ciprofloxacin and a steroid selected from rimexolone, dexamethasone, and fluorometholone.

11. A method according to Claim 9, wherein the composition comprises ciprofloxacin and rimexolone.

12. A method according to Claim 9, wherein the composition comprises ciprofloxacin and dexamethasone.

13. A method according to Claim 9, wherein the composition comprises ciprofloxacin and fluorometholone.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US89/03648

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/56

U.S.Cl.: 514/171

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/171

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A 4 474,751 (HASLAM ET AL) 02 October 1984, see column 4, line 57 - column 5 line 14.	1-13
X	US, A 4 730 013 (BONDI ET AL) 08 March 1988 see column 2 line 35 - column 3, line 15.	1-13
P,X	US, A 4 844 902 (GROHE) 04 July 1989, see column 2 line 41 - column 3, line 17	1-13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 NOVEMBER 1989	10 JAN 1990
International Searching Authority	**Signature of Authorized Officer**
ISA/US	JOSEPH A. LIPOVSKY

Form PCT/ISA/210 (second sheet) (Rev.11-87)